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TITLE: Induction of viral mutation by incorporation of miscoding ribonucleoside analogs into viral RNA

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INVENTOR-INFORMATION:

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CLAIMS:

What is claimed is:
1. A method of increasing the mutation rate of a virus, comprising administering an RNA nucleoside analog to a virally infected cell, wherein the analog is incorporated by a polymerase into an RNA copy of a genomic nucleic acid encoding the virus, said analog replacing a first natural occurring nucleotide having a first complementary nucleotide wherein said analog complements a second nucleotide which is other than the first nucleotide, thereby inducing the virus to mutate.
2. The method of claim 1, wherein the RNA nucleoside analog replaces uracil.
3. The method of claim 1, wherein the RNA nucleoside analog replaces adenine.
4. The method of claim 1, wherein the RNA nucleoside analog replaces cytidine.
5. The method of claim 1, wherein the RNA nucleoside analog replaces guanine.
6. The method of claim 1, wherein the RNA nucleoside analog is incorporated by the polymerase into the RNA copy of the genomic nucleic acid with an efficiency at least about 0.1% that of a naturally occurring complementary nucleic acid.
7. The method of claim 1, wherein the method further includes the proviso that the RNA nucleoside analog is not ribavirin or a 5-halo analog of 1-.beta.-D-ribofuranosylimidazole-4-carboxamide.
8. The method of claim 1 wherein the RNA analog is a non-chain terminating analog.

9. The method of claim 1, wherein the method further includes the proviso that if the virus is HIV, then the RNA nucleoside analog is not HEPT or a 2',5'-bis-O-silylated-3'-spiro-substituted (TSAO) adenine, hypoxanthine, N.sup.1 -alkyl-hypoxanthine, or xanthine or a nucleoside analog that is incorporated and extended at high efficiency by reverse transcriptase of HIV.
10. The method of claim 1, wherein the nucleoside analog is selected from the group consisting of N.sup.4 -aminocytidine, N.sup.1 -methyl-N.sup.4 -aminocytidine, 3,N.sup.4 -ethenocytidine, 3-methylcytidine, 5-hydroxycytidine, N.sup.4 -dimethylcytidine, 5-(2-hydroxyethyl)-cytidine, 5-chlorocytidine, 5-bromocytidine, N.sup.4 -methyl-N.sup.4 -aminocytidine, 5-aminocytidine, 5-nitrosocytidine, 5-(hydroxyalkyl)-cytidine, 5-(thioalkyl)-cytidine and cytidine glycol, 5-hydroxyuridine, 3-hydroxyethyluridine, 3-methyluridine, O.sup.2 -methyluridine, O.sup.2 -ethyluridine, 5-aminouridine, O.sup.4 -methyluridine, O.sup.4 -ethyluridine, O.sup.4 -isobutyluridine, O.sup.4 -alkyluridine, 5-nitrosouridine, 5-(hydroxyalkyl)-uridine, and 5-(thioalkyl)-uridine, 1,N.sup.6 -ethenoadenosine, 3-methyladenosine, and N.sup.6 -methyladenosine, 8-hydroxyguanosine, O.sup.6 -methylguanosine, O.sup.6 -ethylguanosine, O.sup.6

-isopropylguanosine, 3,N.sup.2 -ethenoguanosine, 0.sup.6 -alkylguanosine, 8-oxo-guanosine, 2,N.sup.3 -ethenoguanosine, and 8-aminoguanosine.
11. The method of claim 1, wherein the virus is a retrovirus.
12. The method of claim 1, wherein the polymerase is a human polymerase II.
13. The method of claim 1, wherein the cell is in cell culture.
14. The method of claim 1, wherein the cell is in an animal.
15. The method of claim 1, wherein increasing the mutation rate of the virus produces a progressive loss of viability of the virus.
16. The method of claim 1, comprising administration of more than one species of RNA nucleoside analog to the virally infected cell.
17. The method of claim 1, wherein the virus is an RNA virus selected from the group consisting of hepatitis C, coronavirus, influenza, respiratory syncytial virus and dengue fever.
18. The method of claim 1, wherein the RNA nucleoside analog is an enantio-specific nucleoside analog.
19. A retroviral particle comprising viral genomic RNA, wherein the viral genomic RNA comprises an RNA nucleoside analog.
20. The retroviral particle of claim 19, wherein the particle is an HIV particle.
21. The retroviral particle of claim 19, wherein the nucleoside analog is selected from the group consisting of N.sup.4 -aminocytidine, N.sup.1 -methyl-N.sup.4 -aminocytidine, 3,N.sup.4 -ethenocytidine, 3-methylcytidine, 5-hydroxycytidine, N.sup.4 -dimethylcytidine, 5-(2-hydroxyethyl)-cytidine, 5-chlorocytidine, 5-bromocytidine, N.sup.4 -methyl-N.sup.4 -aminocytidine, 5-aminocytidine, 5-nitrosocytidine, 5-(hydroxyalkyl)-cytidine, 5-(thioalkyl)-cytidine and cytidine glycol, 5-hydroxyuridine, 3-hydroxyethyluridine, 3-methyluridine, O.sup.2 -methyluridine, O.sup.2 -ethyluridine, 5-aminouridine, O.sup.4 -methyluridine, O.sup.4 -ethyluridine, O.sup.4 -isobutyluridine, O.sup.4 -alkyluridine, 5-nitrosouridine, 5-(hydroxyalkyl)-uridine, and 5-(thioalkyl)-uridine, 1,N.sup.6 -ethenoadenosine, 3-methyladenosine, and N.sup.6 -methyladenosine, 8-hydroxyguanosine, O.sup.6 -methylguanosine, O.sup.6 -ethylguanosine, O.sup.6 -isopropylguanosine, 3,N.sup.2 -ethenoguanosine, 0.sup.6 -alkylguanosine, 8-oxo-guanosine, 2,N.sup.3 -ethenoguanosine, and 8-aminoguanosine.
22. A method of increasing the mutation rate of a virus, comprising administering a free base selected from the group comprising adenine, cytosine, guanine, uracil and thymine to a virally infected cell, wherein the base is incorporated by a polymerase into an RNA or DNA copy of a genomic nucleic acid encoding the virus, said base replacing a first natural occurring nucleotide having a first complementary nucleotide wherein said base complements a second nucleotide which is other than the first nucleotide, thereby inducing the virus to mutate.